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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/507,472	09/10/2004	Davide Bellini	50294/012001	3156

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CLARK & ELBING LLP
101 FEDERAL STREET
BOSTON, MA 02110

EXAMINER

KRISHNAN, GANAPATHY

ART UNIT PAPER NUMBER

1623

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/16/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No. 10/507,472	Applicant(s) BELLINI ET AL.	
	Examiner Ganapathy Krishnan	Art Unit 1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 16 February 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-36 and 38-47 is/are pending in the application.
- 4a) Of the above claim(s) 14-36, 38-42 and 47 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 4-12 and 43-46 is/are rejected.
- 7) ☒ Claim(s) 2, 3 and 13 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 10 September 2004 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>10/04/02/05</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Applicant's election without traverse of Group I, claims 1-13 and 43-46, in the reply filed on 2/16/2007 is acknowledged. Claims 14-36, 38-42 and 47 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 2/16/2007.

Specification

The abstract of the disclosure is objected to because the first page of the WIPO publication has been submitted for the abstract. Applicants are requested to kindly file the abstract typed on a separate sheet. Correction is required. See MPEP § 608.01(b).

Claim Objections

Claims 8-9 are objected to because of the following informalities: The recited alcohol and amine in claims 8 and 9 respectively belong to the araliphatic and aliphatic class of compounds. The claims recite other classes too. The other classes of compounds that are not relevant should be deleted from the claims. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

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Claims 1, 4-12 and 44 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an ester of hyaluronic acid formed between the carboxyl group of the hyaluronic acid and the compound of formula (I) having the groups hydroxy, alkyloxy having an alkyl chain C1-C20 bearing one or more hydroxy groups, heterocycle bearing one or more hydroxy groups for R and hydroxy, alkyl C1-C2- substituted with one or more hydroxy and alkyloxy C1-C20 substituted with one or more hydroxy for R1-R3, does not reasonably provide enablement for the said ester for the said substitutions being hydrogen and the alkyl, heterocycle and alkyloxy groups without hydroxy substitutions. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

A conclusion of lack of enablement means that, based on the evidence regarding each of the factors below, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation.

- (A) The breadth of the claims
- (B) The level of one of ordinary skill
- (C) The amount of direction provided by the inventor
- (D) The existence of working examples
- (E) The level of predictability in the art
- (F) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The breadth of the claims

Claim 1 recites, namely R1-R3 being same are selected from the group consisting hydrogen, alkyl C1-C20 possibly substituted with one or more hydroxy groups and alkyloxy C1-C20 possibly substituted with one or more hydroxy groups. This means that R1-R3 can be only

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hydrogens. Also the recitation “possibly substituted” is seen to include the said substitutions without the hydroxy groups. Hence, the claim is seen to embrace compound of formula (I) without any hydroxyl groups. Instant claim 44 is drawn to a composition comprising human fibroblasts and/or a drug added to the said ester. The broad recitation “drug” is seen to embrace any known drug at the time of filing.

The level of one of ordinary skill in the art

The level of skill of those in this art is that of one having experience in organic synthesis/formulation.

The amount of direction provided by the inventor

In the instant case the term drug recited in instant claim is purely a functional distinction that reads on any known or unknown compounds that might have the recited functions. The specification (page 7) recites broad categories of compounds for drugs. The CAFC further clearly states “A written description of an invention requires a precise definition, such as by structural formula or chemical name, of the claimed subject matter sufficient to distinguish it from other materials. One skilled in the art therefore cannot visualize or recognize the identity of the members of the genus. Also the recitation “possibly substituted” is seen to include substitutions without the hydroxy groups for R1-R3.

The existence of working examples

The working examples set forth in the instant specification are drawn to an example of an ester of hyaluronic acid and 2-hydroxy-4-(2-hydroxyethoxy)-2-methyl-propiophenone, a hydrogel of the said ester and a composition of the hydrogel and fibroblasts. One of ordinary

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skill in the art will not extrapolate this to compositions comprising the said ester and any drug or a composition comprising the said ester and drug and fibroblasts as instantly claimed. The ester example is also not representative of all of the substitutions claimed since the said esters as instantly claimed will not form without a hydroxy group present in the compound of formula (I).

The level of Predictability in the Art

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In re Fisher, 427.2d 833, 166 USPQ (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary to satisfy the statute. In the instant case, the instantly claimed invention is highly unpredictable since one of skill in the art cannot fully visualize or recognize the identity of the members of the genus. In the absence of fully recognizing the identity of the members of the genus herein, one of skill in the art would be unable to fully predict possible physiological activities of any compounds having the claimed functional properties in the conjugates herein. Goodman and Gilman's "The Pharmacological Basis of Therapeutics", 10th Ed., 1996, page 54, teaches that the frequency of significant beneficial or adverse drug interactions is unknown (bottom of the left column at page 54). Relatively small changes in the drug level or the type of drug can have significant adverse consequences. In the instant case one of skill in the art would not be able to fully predict possible adverse drug-drug interactions occurring with the many combinations of any compounds having the functional properties in the compositions claimed

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herein. Thus, the teachings of Gillman and Goodman clearly support that the instantly claimed invention is highly unpredictable.

The quantity of experimentation needed to make or use the invention based on the content of the disclosure

Indeed, in view of the information set forth, the instant disclosure is not seen to be sufficient to represent all the combinations encompassed by the recitation of the instant claims. One of ordinary skill in the art would have to carry out undue experimentation to practice the instant invention. Since any structural variation to a compound would be reasonably expected to alter its properties, one of ordinary skill in the art would be required to perform undue experimentation to determine which, if any, other compounds terms "drug" would be useful to make the compositions with the said esters recited in instant claim 44.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 4-12 and 43-46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites hyaluronic acid derivatives. In the absence of the specific derivatizations to the chemical core claimed or distinct language to describe the structural modifications or the chemical names of derivatized of this invention, the identity of the said derivatives would be difficult to describe and the metes and bounds of said derivatives applicants regard as the invention cannot be sufficiently determined because they have not been particularly pointed out

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or distinctly articulated in this and any other claim wherein the said term is recited. Claim 1 is drawn to an ester formed between the carboxyl group of hyaluronic acid and the compound of formula (I). The claim further recites that R1, R2 and R3 can be same (the claim recites the term equal, which is taken to mean the term same) and the Markush members recited are hydrogen, alkyl C1-C20 and alkoxy C1-C20 not substituted (possibly substituted is interpreted as inclusive of not substituted). If R1-R3 are these groups, i.e. compound of formula (I) having substitutions without hydroxy groups, how can the said ester be formed? Formation of an ester requires the reaction of an alcohol component and a carboxylic acid. It is not clear what applicants intend.

Claim 6 recites derivatives which do not comprise C=C bonds but according to the parent claim the resulting ester would have a benzene ring with C=C bonds. Do applicants intend no C=C bonds in the substituents R and R1-R3? Clarification is needed. Claim 6 recites Markush members for the ester derivatives none of which is drawn to the derivative according to parent claim 1, i.e. none of the Markush members is seen as being drawn to ester derivatives that comprise the structural core of formula (I) from the way the claim language is worded. It appears that applicants intend the remaining percentage to be the structural core of formula (I) but the claim language does not clearly convey this. The recitation, "quaternary ammonium salts of N-sulphated or O-sulphated derivatives of hyaluronic acid", does not further limit the parent claim. The claim is also drawn to inner esters of hyaluronic acid but is also seen to include the ester formed between the carboxy of one chain of hyaluronic acid and the hydroxyl groups of another chain. An inner ester is supposed to be the ester formed between the carboxyl and a hydroxyl group in the same chain.

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A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 6 recites the broad recitation cyclic, and the claim also recites cycloaliphatic, which is the narrower statement of the range/limitation. This recitation is also seen in other claims.

Claim 43 is drawn to an ester derivative dissolved in water or in an aqueous solution. It is not clear what applicants intend by this recitation since anything dissolved in water results in an aqueous solution.

Conclusion

1. Claims 1, 4-12 and 43-46 are rejected.
2. Claims 2-3 and 13 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in

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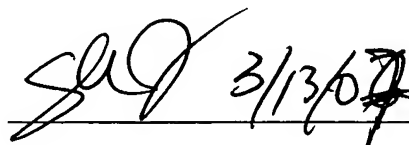
independent form including all of the limitations of the base claim
and any intervening claims.

Any inquiry concerning this communication or earlier communications from the
examiner should be directed to Ganapathy Krishnan whose telephone number is 571-272-0654.
The examiner can normally be reached on 8.30am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's
supervisor, Shaojia A. Jiang can be reached on 571-272-0627. The fax phone number for the
organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent
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system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

GK

Handwritten signature of Shaojia A. Jiang and the date 3/13/07.

Shaojia A. Jiang
Supervisory Patent Examiner
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